~~variation thereof~~. [or a bioequivalent thereof which possesses a high degree of homology therewith and] which is capable of encoding a polypeptide possessing monocyte chemoattractant activity:

CAG CCA GAT GCA ATC AAT ~~GCC CCA~~ GTC ACC TGC TGT TAT AAC
TTC ACC AAT AGG AAG ATC TCA GTG CAG AGG CTC GCG AGC TAT
AGA AGA ATC ACC AGC AAG TGT CCC AAA GAA GCT GTG ATC TTC
AAG ACC ATT GTG GCC AAG GAG ATC TGT GCT GAC CCC AAG CAG
AAG TGG GTT CAG GAT TCC ATG CAG CAC CTG GAC AAG CAA ACC
CAA

wherein,

C is cytosine, T is thymine, A is adenine, and G is guanine.

Claim 11. (Twice Amended)

Lines 2-3, delete ", or the bioequivalent thereof possessing a high degree of homology therewith,"

Lines 4-5, delete "or a biological equivalent thereof possessing a high degree of homology therewith and"

R E M A R K S

Upon entry of the present amendment, claims 1-7 and 9 and 11-25 will be pending in the above-identified application with claims 1-7 and 20-25 being withdrawn from consideration, and claims 9 and

11-19 standing ready for further action on the merits.

The above amendments to the claims do not incorporate new matter into the application. In this regard, the amendments are made in order to more precisely set forth certain cDNA's encompassed by the inventors' discoveries. Based upon such considerations, entry of the present amendment is respectfully requested.

The Examiner rejected claims 9-19 under 35 U.S.C. 112, first and second paragraphs. These rejections of the claims are respectfully traversed and reconsideration and withdrawal thereof are respectfully requested.

Claims 9 and 11 have been amended so that the terminology "or a bioequivalent thereof which possesses a high degree of homology therewith" has been deleted from the claims to the extent it refers to the nucleotide and amino acid sequences recited. Accordingly, withdrawal of the rejection under 35 U.S.C. 112 is required.

The Examiner rejected claims 9-19 under 35 U.S.C. 103 as being unpatentable over Ramb et al, Valente et al or Yoshimura et al for reasons of record. This rejection of the claims is respectfully traversed and reconsideration and withdrawal thereof are respectfully requested based upon the following considerations.

First, submitted herewith under the provisions of 37 C.F.R. 1.132 is a Declaration of one of the present co-inventors, Teizo Yoshimura, which is in accordance with the Court of Custom and Patent Appeals Decision in the case of In re Katz, 687 F2d 450 215

USPQ 14 (1982). In this regard, the accompanying In re Katz Declaration clearly indicates that the Yoshimura et al reference of record from the Journal of Immunology, Volume 142, 1956-1962, No. 6 (1989) is a disclosure of certain aspects of the present invention as claimed by the present co-inventors, and thus that this cited reference is not a disclosure by another within the meaning of 35 U.S.C. 102(a). Accordingly, any rejection of applicants' claims based upon the cited Yoshimura et al reference must be withdrawn.

Regarding the references of Ramb et al and Valente et al, the Examiner bases his rejections on a belief that since each reference discloses a protein possessing monocyte chemotactic activity, one skilled in the art could easily "identify the sequence of an isolated protein". However, as will be discussed further hereinbelow, the prior art does not describe an "isolated protein" and therefore one skilled in the art would not be able to sequence the protein encoded by the cDNA of the present invention even if it was present, albeit in a unique form, in the materials described in the prior art. It is submitted to the Examiner that since neither reference discloses the isolated proteins of the present invention, it is impossible for these references to anticipate or make obvious the present inventions being claimed. Moreover, even if the prior art described the isolated protein of the present invention, the Examiner has not described a detailed cloning strategy which could be employed to clone and sequence the cDNA of the present

invention.

It is submitted to the Examiner that biological fluids often contain many different chemotactic attractants, such as small peptides, different proteins and even non-protein molecules such as leukotrines. In some cases such attractants may be small lipids or peptides bound to a protein. Thus, simply because two different materials from biological fluids possess macrophage chemotactic activity, this does not by itself provide a basis to conclude that such materials are identical or obvious over each other under 35 U.S.C. 102 or 35 U.S.C. 103, respectively; or that cDNA constructs for the production of such different materials would be identical or obvious over each other under the same statutes.

For example, regarding the Ramb et al cited reference, the Abstract thereof simply states that at 27 hours of culture "most activity was found between 10-20,000 (atomic molecular weight)". Likewise, the results obtained after HPLC gel filtration as shown in Figure 4 of the Ramb et al reference, clearly show that chemotactic activity existed in every fraction (but one) of the Ramb et al product for molecular weight fractions of 20-30,000. The authors of the Ramb et al reference even state at page 328 thereof, that "multiple molecular weight species could be identified" in the HPLC fractions. Uncertainty with respect to the products analyzed by Ramb et al also is made evident by their statement at page 328 that "it was obvious that the molecular sieve column was not only separating for size but also for other

molecular properties as can be seen from the fact that activities are still eluting after the marker vitamin B_{12}".

In other words, the Ramb et al authors are indicating that macromolecules were binding to the sieve column and eluting later than the marker position based on size alone, and that therefore no molecular mass estimate could be reliably assigned to any fraction. Moreover, it is noted that the isoelectric focusing performed by Ramb et al showed a remarkable high degree of heterogeneity existed within their product as may be seen upon review of Figure 2 thereof.

Based upon the above considerations, it should be clear that the chemotactic activity observed by Ramb et al was apparently accounted for by many molecules of different molecular mass and isoelectric points, and not by one molecular entity which could be subsequently defined with any precision. As such, the Ramb et al reference cannot anticipate or make obvious applicants' inventions as set forth in claims 9-19, since it is clear that the authors thereof never isolated and identified a polypeptide encompassed by claim 11, which can be encoded by a nucleotide sequence recited in claim 9.

Regarding the cited Valente et al reference, it is reported therein that the purified protein monocyte chemotactic activity had an estimated molecular mass of 14,000. This is different from the peptides produced with the applicants' invention, which possess an estimated molecular mass of about 8,400 Daltons (See pages 4-5 of

applicants' specification). As such, since the Valente et al reference does not report the sequence of the polypeptide produced therein, and moreover discloses a polypeptide possessing a molecular weight much higher than applicants', the same can never anticipate or make obvious applicants' claimed inventions.

Further to the above, it is submitted that the above difference in recited molecular weights for the applicants' protein and the Valente protein is not contradictory with the disclosure of Yoshimura et al and FEBS, Volume 24, No. 2, pages 487-493 (a reference already of record), which states that the Valente protein and applicants' protein have identical amino acid compositions. This is true, since amino acid compositions are always reported as a relative number (i.e., a percentage or a ratio) whereas molecular weights are always reported as an absolute number (i.e., atomic molecular weights or Daltons).

MCP-1 belongs to a family of proteins which are characterized by similar molecular weights and almost identical location of 4 half-cystines. Recently two other proteins which also belong to the same family, RANTES and I-309, have been reported to be chemotactic for human monocytes (Schall et al, Science, 347:669, 1990; Miller et al, Proc. Natl. Acad. Sci., USA 89:2950, 1992). These two proteins have similar molecular weights and basic isoelectric points, and are secreted by peripheral blood mononuclear leukocytes. The two proteins could exist in the culture supernatants of mitogen-stimulated human mononuclear leukocytes

which Ramb et al used for the experiment. Therefore, the monocyte chemotactic activity reported by Ramb et al could be RANTES or I-309. It is impossible to say that the activity reported by Ramb et al was identical to MCP-I without further purification of the activity. On the other hand, the present inventors purified MCP-1 from a human malignant glioma cell line which does not seem to secrete RANTES or I-309. Moreover, as evidenced in a recent review on MCP-1 (Yoshimura and Leonard, Cytokines, Volume 4, page 131, 1992, Karger, Basel), MCP-1 was found when the present inventors were working on another chemo-attractant (monocyte-derived neutrophil chemotactic factor, MDNCF). These factors further support the novelty and non-obviousness of the inventors' discoveries over the cited references.

Based upon each of the above considerations, the Examiner is respectfully requested to withdraw all outstanding rejections of the inventors' claims under 35 U.S.C. 112 and 35 U.S.C. 103. Moreover, an early allowance of the claims is earnestly solicited.

Pursuant to 37 C.F.R. 1.17 and 1.136(a), applicants respectfully petition for a one (1) month extension of time for filing a response in connection with the above-identified application and the required fee of $110.00 is attached hereto.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account Number 02-2448.

Respectfully submitted,

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(1173-145P, SN 07/330,446)
Enclosure - Declaration under 37 C.F.R. 1.132 by Dr. Yoshimura.